General

Guideline Title

Clinical practice guideline on diagnosis and treatment of hyponatraemia.

Bibliographic Source(s)

Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn EJ, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, van der Veer S, Van Biesen W, Nagler E, Hyponatraemia Guideline Development Group. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Nephrol Dial Transplant. 2014 Apr;29 Suppl 2:i1-i39. [247 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The strength of the recommendations (1, 2) and the quality of evidence (A-D) are defined at the end of the "Major Recommendations" field.

Diagnosis of Hyponatraemia

Classification of Hyponatraemia

Definition of Hyponatraemia Based on Biochemical Severity

- The guideline development group (GDG) defines 'mild' hyponatraemia as a biochemical finding of a serum sodium concentration between 130 and 135 mmol/l as measured by ion-specific electrode.
- The GDG defines 'moderate' hyponatraemia as a biochemical finding of a serum sodium concentration between 125 and 129 mmol/l as measured by ion-specific electrode.
- The GDG defines 'profound' hyponatraemia as a biochemical finding of a serum sodium concentration <125 mmol/l as measured by ion-specific electrode.

Definition of Hyponatraemia Based on Time of Development

- The GDG defines 'acute' hyponatraemia as hyponatraemia that is documented to exist <48 h.
- The GDG defines 'chronic' hyponatraemia as hyponatraemia that is documented to exist for at least 48 h.
- If hyponatraemia cannot be classified, the GDG considers it being chronic, unless there is clinical or anamnestic evidence of the contrary

(see Table 8 in the original guideline document).

Definition of Hyponatraemia Based on Symptoms

- The GDG defines 'moderately symptomatic' hyponatraemia as any biochemical degree of hyponatraemia in the presence of moderately severe symptoms of hyponatraemia (see Table 5 in the original guideline document).
- The GDG defines 'severely symptomatic' hyponatraemia as any biochemical degree of hyponatraemia in the presence of severe symptoms of hyponatraemia (see Table 5 in the original guideline document).

Confirming Hypotonic and Excluding Non-hypotonic Hyponatraemia

- The GDG recommends excluding hyperglycaemic hyponatraemia by measuring the serum glucose concentration and correcting the measured serum sodium concentration for the serum glucose concentration if the latter is increased (1D).
- Hyponatraemia with a measured osmolality <275 mOsm/kg always reflects hypotonic hyponatraemia (not graded).
- Accept as 'hypotonic hyponatraemia' a hyponatraemia without evidence for causes of nonhypotonic hyponatraemia as listed in Table 10 in the original guideline document (not graded).

Which Parameters to Be Used for Differentiating Causes of Hypotonic Hyponatraemia?

- The GDG recommends interpreting urine osmolality of a spot urine sample as a first step (1D).
- If urine osmolality is ≤100 mOsm/kg, the GDG recommends accepting relative excess water intake as a cause of the hypotonic hyponatraemia (1D).
- If urine osmolality is >100 mOsm/kg, the GDG recommends interpreting the urine sodium concentration on a spot urine sample taken simultaneously with a blood sample (1D).
- If urine sodium concentration is ≤30 mmol/l, the GDG suggests accepting low effective arterial volume as a cause of the hypotonic hyponatraemia (2D).
- If urine sodium concentration is >30 mmol/l, the GDG suggests assessing extracellular fluid status and use of diuretics to further differentiate likely causes of hyponatraemia (2D).
- The GDG suggests against measuring vasopressin for confirming the diagnosis of syndrome of inappropriate antidiuretic hormone secretion (SIADH) (2D).

Treatment of Hypotonic Hyponatraemia

Hyponatraemia with Severe Symptoms

First-hour Management, Regardless of Whether Hyponatraemia Is Acute or Chronic

- The GDG recommends prompt intravenous (i.v.) infusion of 150 ml 3% hypertonic over 20 min (1D).
- The GDG suggests checking the serum sodium concentration after 20 min while repeating an infusion of 150 ml 3% hypertonic saline for the next 20 min (2D).
- The GDG suggests repeating the above recommendations twice or until a target of 5 mmol/l increase in serum sodium concentration is achieved (2D).
- Manage patients with severely symptomatic hyponatraemia in an environment where close biochemical and clinical monitoring can be provided (not graded).

Follow-up Management in Case of Improvement of Symptoms After a 5 mmol/l Increase in Serum Sodium Concentration in the First Hour, Regardless of Whether Hyponatraemia Is Acute or Chronic

- The GDG recommends stopping the infusion of hypertonic saline (1D).
- The GDG recommends keeping the i.v. line open by infusing the smallest feasible volume of 0.9% saline until cause-specific treatment is started (1D).
- The GDG recommends starting a diagnosis-specific treatment if available, aiming at least to stabilise sodium concentration (1D).
- The GDG recommends limiting the increase in serum sodium concentration to a total of 10 mmol/l during the first 24 h and an additional 8 mmol/l during every 24 h thereafter until the serum sodium concentration reaches 130 mmol/l (1D).
- The GDG suggests checking the serum sodium concentration after 6 and 12 h and daily afterwards until the serum sodium concentration has stabilised under stable treatment (2D).

Follow-up Management in Case of No Improvement of Symptoms After a 5 mmol/l Increase in Serum Sodium Concentration in the First

Hour, Regardless of Whether Hyponatraemia Is Acute or Chronic

- The GDG recommends continuing an i.v. infusion of 3% hypertonic saline or equivalent aiming for an additional 1 mmol/l per h increase in serum sodium concentration (1D).
- The GDG recommends stopping the infusion of 3% hypertonic saline or equivalent when the symptoms improve, the serum sodium concentration increases 10 mmol/l in total or the serum sodium concentration reaches 130 mmol/l, whichever occurs first (1D).
- The GDG recommends additional diagnostic exploration for other causes of the symptoms than hyponatraemia (1D).
- The GDG suggests checking the serum sodium concentration every 4 h as long as an i.v. infusion of 3% hypertonic saline or equivalent is continued (2D).

Hyponatraemia with Moderately Severe Symptoms

- The GDG recommends starting prompt diagnostic assessment (1D).
- Stop, if possible, medications and other factors that can contribute to or provoke hyponatraemia (not graded).
- The GDG recommends cause-specific treatment (1D).
- The GDG suggests immediate treatment with a single i.v. infusion of 150 ml 3% hypertonic saline or equivalent over 20 min (2D).
- The GDG suggests aiming for a 5 mmol/l per 24-h increase in serum sodium concentration (2D).
- The GDG suggests limiting the increase in serum sodium concentration to 10 mmol/l in the first 24 h and 8 mmol/l during every 24 h thereafter, until a serum sodium concentration of 130 mmol/l is reached (2D).
- The GDG suggests checking the serum sodium concentration after 1, 6 and 12 h (2D).
- The GDG suggests additional diagnostic exploration for other causes of the symptoms if the symptoms do not improve with an increase in serum sodium concentration (2D).
- The GDG suggests considering to manage the patient as in severely symptomatic hyponatraemia if the serum sodium concentration further decreases despite treating the underlying diagnosis (2D).

Acute Hyponatraemia Without Severe or Moderately Severe Symptoms

- Make sure that the serum sodium concentration has been measured using the same technique used for the previous measurement and that no administrative errors in sample handling have occurred (not graded).
- If possible, stop fluids, medications and other factors that can contribute to or provoke hyponatraemia (not graded).
- The GDG recommends starting prompt diagnostic assessment (1D).
- The GDG recommends cause-specific treatment (1D).
- If the acute decrease in serum sodium concentration exceeds 10 mmol/l, the GDG suggests a single i.v. infusion of 150 ml 3% hypertonic saline or equivalent over 20 min (2D).
- The GDG suggests checking the serum sodium concentration after 4 h, using the same technique as used for the previous measurement (2D).

Chronic Hyponatraemia Without Severe or Moderately Severe Symptoms

General Management

- Stop non-essential fluids, medications and other factors that can contribute to or provoke hyponatraemia (not graded).
- The GDG recommends cause-specific treatment (1D).
- In mild hyponatraemia, the GDG suggests against treatment with the sole aim of increasing the serum sodium concentration (2C).
- In moderate or profound hyponatraemia, the GDG recommends avoiding an increase in serum sodium concentration of >10 mmol/l during the first 24 h and >8 mmol/l during every 24 h thereafter (1D).
- In moderate or profound hyponatraemia, the GDG suggests checking the serum sodium concentration every 6 h until the serum sodium concentration has stabilised under stable treatment (2D).
- In case of unresolved hyponatraemia, reconsider the diagnostic algorithm and ask for expert advice (not graded).

Patients with Expanded Extracellular Fluid

- The GDG recommends against a treatment with the sole aim of increasing the serum sodium concentration in mild or moderate hyponatraemia (1C).
- The GDG suggests fluid restriction to prevent further fluid overload (2D).
- The GDG recommends against vasopressin receptor antagonists (1C).
- The GDG recommends against demeclocycline (1D).

Patients with SIAD

- In moderate or profound hyponatraemia, the GDG suggests restricting fluid intake as first-line treatment (2D).
- In moderate or profound hyponatraemia, the GDG suggests the following can be considered equal second-line treatments: increasing solute intake with 0.25–0.50 g/kg per day of urea or a combination of low-dose loop diuretics and oral sodium chloride (2D).
- In moderate or profound hyponatraemia, the GDG recommends against lithium or demeclocycline (1D).
- In moderate hyponatraemia, the GDG does not recommend vasopressin receptor antagonists (1C).
- In profound hyponatraemia, the GDG recommends against vasopressin receptor antagonists (1C).

Patients with Reduced Circulating Volume

- The GDG recommends restoring extracellular volume with i.v. infusion of 0.9% saline or a balanced crystalloid solution at 0.5–1.0 ml/kg per h (1B).
- Manage patients with haemodynamic instability in an environment where close biochemical and clinical monitoring can be provided (not graded).
- In case of haemodynamic instability, the need for rapid fluid resuscitation overrides the risk of an overly rapid increase in serum sodium concentration (not graded).

What to Do if Hyponatraemia Is Corrected Too Rapidly?

- The GDG recommends prompt intervention for relowering the serum sodium concentration if it increases >10 mmol/l during the first 24 h or >8 mmol/l in any 24 h thereafter (1D).
- The GDG recommends discontinuing the ongoing active treatment (1D).
- The GDG recommends consulting an expert to discuss if it is appropriate to start an infusion of 10 ml/kg body weight of electrolyte-free water (e.g., glucose solutions) over 1 h under strict monitoring of urine output and fluid balance (1D).
- The GDG recommends consulting an expert to discuss if it is appropriate to add i.v. desmopressin 2 µg, with the understanding that this should not be repeated more frequently than every 8 h (1D).

Definitions

Implications of Strong and Weak Recommendations for Stakeholders

Grade	Implications		
	Patients	Clinicians	Policy
1: Strong, "The Guideline Development Group recommends"	Most people in your situation would want the recommended course of action, only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be adopted as a policy in most situations.
2: Weak, "The Guideline Development Group suggests"	Most people in your situation would want the recommended course of action, but many would not.	You should recognize that different choices will be appropriate for different patients. You must help each patient to arrive at a management decision consistent with her or his values and preferences.	Policy-making will require substantial debate and involvement of many stakeholders.

Note: Adapted from Guyatt GH, Oxman AD, Vist GE et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.

The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counselling and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements but are not meant to be interpreted as being stronger recommendations than level 1 or 2 recommendations.

Grade for the Overall Quality of Evidence

Grade	Quality Level	Description
A	High	The authors are confident that the true effects lie close to those of the estimates of the effect.
B	Moderate	The true effects are likely to be close to the estimates of the effects, but there is a possibility that they are substantially different.
C	Low	The true effects might be substantially different from the estimates of effects.
D	Very Low	The estimates are very uncertain and will often be far from the truth.

Note: Adapted from Guyatt GH, Oxman AD, Vist GE et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.

Clinical Algorithm(s)

The following algorithms are available in the original guideline document:

- Algorithm for the diagnosis of hyponatraemia
- Algorithm for the management of hypotonic hyponatraemia

Scope

Disease/Condition(s)

Hyponatraemia

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Emergency Medicine

Endocrinology

Internal Medicine

Nephrology

Surgery

Intended Users

Health Care Providers

Hospitals

Physician Assistants

Physicians

Guideline Objective(s)

To provide guidance on the diagnosis and treatment of adult individuals with hypotonic hyponatraemia

Target Population

Adult patients with acute or chronic hypotonic hyponatraemia

Interventions and Practices Considered

Diagnosis/Evaluation

1. Definition based on biochemical severity (mild, moderate, profound)
2. Definition based on time of development (acute, chronic)
3. Definition based on symptoms (moderately symptomatic, severely symptomatic)
4. Confirmation of hypotonic and exclusion of non-hypotonic hyponatraemia
5. Differentiation of causes of hypotonic hyponatraemia

Management/Treatment

1. Intravenous (i.v.) saline
2. Monitoring of serum sodium concentration
3. Close biochemical and clinical monitoring
4. Follow-up management in case of improvement of symptoms
5. Cause-specific treatment
6. Cessation of fluids, medications and other factors that can contribute to hyponatraemia
7. Fluid restriction
8. Oral urea
9. Low-dose loop diuretics and oral sodium chloride combination
10. Restoration of extracellular volume (as indicated)
    - i.v. 0.9% saline
    - Balanced crystalloid solution
11. Relowering sodium if hyponatraemia is corrected too rapidly
    - Consultation with an expert
    - i.v. desmopressin
    - Electrolyte-free water

Note: Lithium and demeclocycline were considered but not recommended for treatment of hyponatraemia.

Major Outcomes Considered

- Patient survival
- Coma
- Brain damage/brain oedema
- Epileptic seizures
- Osmotic demyelinating syndrome
- Respiratory arrest
- Quality of life

- Cognitive function

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Developing Clinical Questions

From the final scope of the guideline, specific research questions, for which a systematic review would be conducted, were identified.

Diagnosis and Differential Diagnosis of Hypotonic Hyponatraemia

1. In patients with hypotonic hyponatraemia, how accurate are various 'diagnostic strategies' in comparison with a reference test of infusing 2 l 0.9% sodium chloride solution for differentiating hypovolaemic from euvolaemic hyponatraemia?
2. In patients with hypotonic hyponatraemia, how accurate are various 'diagnostic strategies' in comparison with a reference test of expert panel diagnosis in differentiating hypovolaemic from euvolaemic hyponatraemia?

Acute and Chronic Treatment of Hypotonic Hyponatraemia

1. In patients with hypotonic hyponatraemia, which treatments are effective in improving outcomes?
2. In patients with hypotonic hyponatraemia, does the change in serum sodium concentration per unit time influence outcomes?

Development of Review Questions

The methods support team assisted in developing review questions, i.e., framing the clinical questions into a searchable format. This required careful specification of the patient group (P), the intervention (I), the comparator (C) and the outcomes (O) for intervention questions and the patient group, index tests, reference standard and target condition for questions of diagnostic test accuracy. For each question, the guideline development group (GDG) agreed on explicit review question criteria including study design features (see Appendices 1 and 2 [see the "Availability of Companion Documents" field] for Detailed Review Questions and PICO tables).

Searching for Evidence

Sources

The European Renal Best Practice (ERBP) methods support team searched The Cochrane Database of Systematic Reviews (May 2011), The Database of Abstracts of Reviews of Effects (DARE; May 2011), The Cochrane Central Register of Controlled Trials (CENTRAL; May 2011) and MEDLINE (1946 to May, Week 4, 2011) for questions on both diagnosis and treatment. To identify the limits for the increase in serum sodium concentration above which the risk of osmotic demyelination starts to rise, the GDG searched MEDLINE database from 1997 onwards under the assumption that earlier reports would describe more dramatic increases and would not contribute to helping set an upper limit. All searches were updated on 10th December 2012. The search strategies combined subject headings and text words for the patient population, index test and target condition for the diagnostic questions and subject headings and text words for the population and intervention for the intervention questions. The detailed search strategies are available in Appendix 3 (see the "Availability of Companion Documents" field).

Reference lists from included publications were screened to identify additional papers. The methods support team also searched guideline databases and organisations including the National Guideline Clearinghouse (NGC), Guidelines International Network, Guidelines Finder, Centre for Reviews and Dissemination, National Institute for Health and Care Excellence (NICE), and professional societies of Nephrology, Endocrinology and Intensive Care Medicine for guidelines to screen the reference lists.

Selection

For diagnostic questions, the GDG included every study that compared any of the predefined clinical or biochemical tests with infusion of 2 10.9% saline as a reference test or with an expert panel for differentiating hypovolaemic from euvolaemic hyponatraemia. For questions on treatment strategies, every study in which one of the predefined medications was evaluated in humans was included. Case series that reported on benefit were excluded if the number of participants was ≤5 but included even individual case reports if they reported an adverse event. No restriction was made based on language. For identifying the limits for the increase in serum sodium concentration above which the risk of osmotic demyelination starts to rise, all observational studies reporting cases of osmotic demyelinating syndrome and corresponding serum sodium concentration correction speeds were included.

A member of the ERBP methods support team screened all titles and abstracts to discard the clearly irrelevant ones. All members of the GDG completed a second screening. All abstracts that did not meet the inclusion criteria were discarded. Any discrepancies at this stage were resolved by group consensus.

The methods support team retrieved full texts of potentially relevant studies and two reviewers examined them for eligibility independently of each other. The reviewer duos always consisted of one content specialist and one methodologist from the ERBP methods support team. Any discrepancies were resolved by consensus. If no consensus could be reached, the disagreement was settled by group arbitrage.

Number of Source Documents

Study selection flow charts are provided in Appendix 5 (see the Availability of Companion Documents" field).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grade for the Overall Quality of Evidence

Grade	Quality Level	Description
A	High	The authors are confident that the true effects lie close to those of the estimates of the effect.
B	Moderate	The true effects are likely to be close to the estimates of the effects, but there is a possibility that they are substantially different.
C	Low	The true effects might be substantially different from the estimates of effects.
D	Very Low	The estimates are very uncertain and will often be far from the truth.

Note: Adapted from Guyatt GH, Oxman AD, Vist GE et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction and Critical Appraisal of Individual Studies

For each included study, the guideline development group (GDG) collected relevant information on design, conduct and relevant results through

standardised data extraction forms in Microsoft Excel (2010). As part of an ongoing process of introducing software to facilitate the guideline development process, the European Renal Best Practice (ERBP) methods support team used two formats for data extraction and collation. For detailed methods, see Appendices 4 and 5 (see the "Availability of Companion Documents" field). Briefly, the GDG used both a simple spreadsheet format and a more sophisticated version, which incorporated user forms programmed in Visual Basic. For each question, two reviewers extracted all data independently of each other. The GDG produced tables displaying the data extraction of both reviewers. Both reviewers checked all data independently of each other. Any discrepancies were resolved by consensus and if no consensus could be reached, disagreements were resolved by an independent referee. From these tables, merged consensus evidence tables were produced for informing the recommendations. The evidence tables are available in Appendices 6 and 7 (see the "Availability of Companion Documents" field).

Risk of bias of the included studies was evaluated using various validated checklists, as recommended by the Cochrane Collaboration. These were AMSTAR for Systematic Reviews, the Cochrane Risk of Bias tool for randomised controlled trials, the Newcastle Ottawa scale for cohort and case–control studies and the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) for diagnostic test accuracy studies. Data were compiled centrally by the ERBP methods support team.

Evidence Profiles

The evidence for outcomes on therapeutic interventions from included systematic reviews and randomised controlled trials was presented using the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The evidence profiles include details of the quality assessment as well as summary – pooled or unpooled – outcome data, an absolute measure of intervention effect when appropriate and the summary of quality of evidence for each outcome. Evidence profiles were constructed by the methods support team and reviewed and confirmed with the rest of the GDG. Evidence profiles were constructed for research questions addressed by at least two randomised controlled trials. If the body of evidence for a particular comparison of interest consisted of only one randomised controlled trial or of solely observational data, the summary tables provided the final level of synthesis.

Rating the Quality of the Evidence for Each Outcome Across Studies

In accordance with GRADE, the GDG initially categorised the quality of the evidence for each outcome as high if it originated predominantly from randomised controlled trials and low if it originated from observational data. The GDG subsequently downgraded the quality of the evidence one or two levels if results from individual studies were at serious or very serious risk of bias, there were serious inconsistencies in the results across studies, the evidence was indirect, the data were sparse or imprecise or publication bias thought to be likely. If evidence arose from observational data, but effect sizes were large, there was evidence of a dose–response gradient or all plausible confounding would either reduce a demonstrated effect or suggest a spurious effect when results showed no effect, they would upgrade the quality of the evidence (see Table 2 in the original guideline document). Uncontrolled case series and case reports automatically received downgrading from low to very low level of evidence for risk of bias, so that no other reasons for downgrading were marked. By repeating this procedure, the GDG would obtain an overall quality of the evidence for each outcome and each intervention.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Establishment of the Guideline Development Group

The councils of the three participating societies, European Society of Intensive Care Medicine (ESICM), European Society of Endocrinology (ESE) and European Renal Best Practice (ERBP), selected the co-chairs of the guideline development group (GDG). The co-chairs then assembled the steering committee with representatives of the three societies involved in this joint venture. This steering committee convened in October 2010 and decided on the composition of the GDG, taking into account the clinical and research expertise of the proposed candidates. The GDG consisted of content experts, which included individuals with expertise in hyponatraemia, endocrinology, general internal medicine, intensive care medicine and clinical nephrology as well as an expert in systematic review methodology. The ERBP methods support team provided methodological input and practical assistance throughout the guideline development process.

Formulating Statements and Grading Recommendations

After the summary tables were produced and evidence profiles had been prepared, revised and approved by the GDG, two full-weekend plenary meetings were held in September 2012 and December 2012 to formulate and grade the recommendations.

Recommendations can be for or against a certain strategy. The GDG drafted the recommendations based on their interpretation of the available evidence. Judgements around four key factors determined the strength of a recommendation: the balance between desirable and undesirable consequences of alternative therapeutic or diagnostic strategies, the quality of the evidence, the variability in values and preferences. The GDG did not conduct formal decision or cost analysis. In accordance to GRADE, the strength of the recommendations are classified as strong, coded '1' or weak, coded '2' (see the "Rating Scheme for the Strength of the Recommendations" field). Individual statements were made and discussed in an attempt to reach group consensus. If the GDG could not reach consensus, they held a formal open vote by show of hands. An arbitrary 80% had to cast a positive vote for a statement to be accepted. Voting results and reasons for disagreement were specified in the rationale.

Ungraded Statements and Advice for Clinical Practice

The GDG decided to use an additional category of ungraded statements for areas where formal evidence was not sought and statements were based on common sense or expert experience alone. They were termed 'statement' to differentiate them from graded recommendations and do not hold an indicator for the quality of the evidence. The ungraded statements were generally written as simple declarative statements but were not meant to be stronger than level 1 or 2 recommendations.

Also provided was additional advice for clinical practice. The advice is not graded and is only for the purpose of improving practical implementation. It contains some elaboration on one of the statements, clarifying how the statement can be implemented in clinical practice.

Writing Rationale

The GDG collated recommendations and ungraded statements for each of the clinical questions in separate sections structured according to a specific format. Each question resulted in one or more specific boxed statements. Within each recommendation, the strength was indicated as level 1 or 2 and the quality of the supporting evidence as A, B, C or D as prescribed by the GRADE methodology (see the "Rating Scheme for the Strength of the Evidence" field).

These statements are followed by advice for clinical practice where relevant and the rationale. The rationale contains a brief section on 'why this question' with relevant background and justification of the topic, followed by a short narrative review of the evidence in 'what did the GDG find' and finally a justification of how the evidence translated in the recommendations made in 'how did the GDG translate the evidence into the statement'.

When areas of uncertainty were identified, the GDG considered making suggestions for future research based on the importance to patients or the population and on ethical and technical feasibility.

Rating Scheme for the Strength of the Recommendations

Implications of Strong and Weak Recommendations for Stakeholders

Grade	Implications		
	Patients	Clinicians	Policy
1: Strong, "The Guideline Development Group recommends"	Most people in your situation would want the recommended course of action, only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be adopted as a policy in most situations.
2: Weak, "The Guideline Development Group suggests"	Most people in your situation would want the recommended course of action, but many would not.	You should recognize that different choices will be appropriate for different patients. You must help each patient to arrive at a management decision consistent with her or his values and preferences.	Policy-making will require substantial debate and involvement of many stakeholders.

Note: Adapted from Guyatt GH, Oxman AD, Vist GE et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.

The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counselling and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements but are not meant to be interpreted as being stronger recommendations than level 1 or 2 recommendations.

Cost Analysis

The guideline development group (GDG) did not conduct formal cost analysis.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Internal and External Review

Internal Review

A first draft of the guideline was sent to a selected group of internal reviewers. Each society nominated experts in hyponatraemia and/or members of their governance body. Internal reviewers were asked to complete a grid-based evaluation of overall appreciation of each individual statement, using a score between 1 and 5. These scores were averaged and colour-coded between red and green to help visualise any problematic part. In addition, internal reviewers were asked to comment on the statements and the rationale within free text fields limited to 225 characters. All these comments and suggestions were discussed during an additional meeting of the guideline development group (GDG) in June 2013. For each comment or suggestion, the GDG evaluated whether it was needed to adapt the statement, again taking into account the balance between desirable and undesirable consequences of the alternative management strategies, the quality of the evidence and the variability in values and preferences.

External Review

The guideline was sent to the Endocrine Society of Australia (ESA) and the Kidney Health Australia–Caring for Australasians with Renal Impairment (KHA–CARI) for review. Reviewers could use free text to suggest amendments and/or fill in a matrix questionnaire in Microsoft Excel. In addition, all members of the European Renal Association – European Dialysis and Transplant Association (ERA–EDTA) received an online questionnaire with a standardised answer form in Microsoft Excel. ERA–EDTA members were asked to express to what extent they believed the individual statements were clear, implementable and to what extent they agreed with the content on a scale from 1 to 5. In addition, a free text field was provided to allow for additional comments. All these valid comments and suggestions were discussed with the GDG through e-mail and during a final meeting of the co-chairs of the GDG, the methods support team and the chair of the European Renal Best Practice (ERBP).

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Accurate diagnosis and appropriate treatment of hyponatraemia

See the "Rationale" sections in the original guideline document for benefits of specific interventions.

Potential Harms

- Adverse effects associated with treatment
- Osmotic demyelination syndrome is a rare but dramatic complication that occurs in chronic hyponatraemia when the serum sodium concentration increases too rapidly.

See the "Rationale" sections in the original guideline document for harms of specific interventions.

Qualifying Statements

Qualifying Statements

The purpose of this Clinical Practice Guideline was to provide guidance on the diagnosis and treatment of adult individuals with hypotonic hyponatraemia. It was designed to provide information and assist in decision-making related to this topic. It was not intended to define a standard of care and should not be construed as one. It should not be interpreted as prescribing an exclusive course of management.

Implementation of the Guideline

Description of Implementation Strategy

Optimizing Implementation

Recommendations often fail to reach implementation in clinical practice partly because of their wording. As part of a research project to evaluate methods for improving guideline development processes, the guideline development group (GDG) integrated the GuideLine Implementability Appraisal (GLIA) instrument to optimise the wording of the recommendations. The tool primarily enables structured evaluation of factors such as executability (is it clear from the statement exactly what to do) and decidability (exactly under what conditions) of preliminary recommendations. In addition, the tool is designed to highlight other problems possibly hindering implementation, e.g., recommendations being inconsistent with clinicians' existing beliefs or patients' expectations. The appraisal was done by a panel of target guideline users external to the GDG. Comments and remarks were communicated to the GDG and used to help refine the recommendations.

Implementation Tools

Clinical Algorithm

Foreign Language Translations

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn EJ, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, van der Veer S, Van Biesen W, Nagler E, Hyponatraemia Guideline Development Group. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Nephrol Dial Transplant. 2014 Apr;29 Suppl 2:i1-i39. [247 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Apr

Guideline Developer(s)

European Renal Best Practice - Independent Expert Panel

Source(s) of Funding

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Guideline Committee

Guideline Development Group

Composition of Group That Authored the Guideline

Guideline Development Group Members: Goce Spasovski (*Co-chair*), State University Hospital Skopje, Skopje, Macedonia; Raymond Vanholder (*Co-chair*), Ghent University Hospital, Ghent, Belgium; Bruno Allolio, Würzburg University Hospital, Würzburg, Germany; Djillali Annane, Raymond Poincaré Hospital, University of Versailles Saint Quentin, Paris, France; Steve Ball, Newcastle Hospitals and Newcastle University, Newcastle, UK; Daniel Bichet, Sacré-Coeur Hospital, University of Montreal, Montreal, Quebec, Canada; Guy Decaux, Erasmus University Hospital, Brussels, Belgium; Wiebke Fenske, Würzburg University Hospital, Würzburg, Germany; Ewout J. Hoorn, Erasmus Medical Centre, Rotterdam, The Netherlands; Carole Ichai, Nice University Hospital, Nice, France; Michael Joannidis, Innsbruck University Hospital, Innsbruck, Austria; Alain Soupart, Erasmus University Hospital, Brussels, Belgium; Robert Zietse, Erasmus Medical Centre, Rotterdam, The Netherlands; Maria Haller, Specialist Registrar Nephrology, KH Elisabethinen Linz, Linz, Austria; Evi Nagler, Specialist Registrar Nephrology, Ghent University Hospital, Ghent, Belgium; Wim Van Biesen, Consultant Nephrologist, Chair of ERBP, Ghent University Hospital, Ghent, Belgium; Sabine van der Veer, Implementation Specialist, Amsterdam Medical Centre Amsterdam, The Netherlands

Financial Disclosures/Conflicts of Interest

Declaration of Interest

All participants in the guideline development group (GDG) were required to fill out a detailed 'Declaration of interest' including all the current and future conflicts of interest as well as past interest restricted to the 2 years before joining the guideline development process. Because it was judged that excluding every individual with some degree of potential conflict of interest would make assembling a GDG impossible, members of the GDG were allowed to have past financial and/or intellectual conflicts of interest. No consequences were attached to the stated interests, but rather insisted on transparency. All members of the GDG were allowed to participate in all the discussions and have equal weight in formulating the statements. All were allowed equal involvement in data extraction and writing the rationales. The declaration of interest forms are available from www.european-renal-best-practice.org/content/Joint-workgroup-hyponatraemia and are updated on a regular basis.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Nephrology Dialysis Transplantation Journal Web site.

Availability of Companion Documents

The following are available:

- Clinical practice guideline on diagnosis and treatment of hyponatraemia. Supplementary data. 2014 Apr. Available from the Nephrology Dialysis Transplantation Journal Web site.
- Nagler EV, Webster AC, Bolignano D, Haller MC, Nistor I, van der Veer SN, Fouque D, Van Biesen W. European Renal Best Practice (ERBP) guideline development methodology: towards the best possible guidelines. Nephrol Dial Transplant 2014 Apr;29(4):731–8. Available from the Nephrology Dialysis Transplantation Journal Web site.

A field version (summary) is available in a variety of languages from the European Renal Best Practices Web site.

Patient Resources

None available

NGC Status

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